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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/580,987	ZHANG ET AL.	
	Examiner	Art Unit	
	MARIA LEAVITT	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34-55 and 62-67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-55 and 62-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *08-29-08;12-31-07;10-04-06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
2. Applicants' amendment filed on 11-04-2008 has been entered.
3. Status of claims. Claims 34-55 and 62-67 are pending. Claims 34 and 41 have been amended and claims 62-67 have been added by Applicants' amendment filed on 11-04-2008. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.
4. Therefore, claims 34-55 and 62-67 are currently being examined to which the following grounds of rejection are applicable.

Response to arguments

Withdrawn objections in response to Applicant arguments or amendments

In view of Applicants' amendment of the specification at pages 2, 8 and 9, objection to the specification has been withdrawn.

Claim Rejections - 35 U.S.C. § 112

In view of Applicants' amendment of claim 41, subpart d, to delete the term "substantially", rejection of claim 41 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, has been withdrawn.

In view of the withdrawn rejection, applicant's arguments are rendered moot.

Objections/Rejections maintained in response to Applicant arguments or amendments

Claim objection

Claim 35 remain objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 35 recites, "a tryptophan analog". However, claim 34 has been amended to recite "5-substituted tryptophan". Tryptophan analogs are not necessary all 5-substituted tryptophan analogs as they can be substituted at other positions, e.g., the 7-azatryptophan or Methyl-DL-tryptophan, beta-(3-benzofuranyl)-DL-alanine.

Response to Applicants' arguments as they apply to objection of claim 35

At page 7 of remarks applicants argue that the objected term in claim 35 has been deleted. Such is not persuasive.

The phrase "a tryptophan analog" is recited in claim 35.

Claim Rejections - 35 USC § 112 – Scope of enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 34-55 remain rejected and new claims 62-67 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method of incorporating a 5-substituted tryptophan unnatural amino acid into a peptide, the method comprising,

preparing a construct comprising a nucleic acid sequencing consisting of SEQ ID No. 1 encoding the orthogonal mutant tryptophanyl-tRNA synthetase (O-muTrpRS) of SEQ ID No. 2,

preparing a construct comprising nucleic acid sequencing consisting of SEQ ID No. 3 encoding a orthogonal tRNA (O-tRNA),

introducing into a mammalian cell the O-muTrpRS construct and the O-tRNA construct and preferentially aminoacylating the expressed O-tRNA with the 5-subtituted tryptophan unnatural amino acid, wherein said aminoacylation is catalyzed by the expressed O-muTrpRS,

does not reasonably provide enablement for a genus of unspecified orthogonal aminoacyl-tRNA synthetase **conservative** variants of SEQ ID NO: 2 (e.g., the O-muTrpRS polynucleotide sequence of SEQ ID NO: 1 encodes the amino acid sequence of SEQ ID NO: 2), and a genus of undetermined O-tRNA, wherein O-RS preferentially aminoacylates a O-tRNA with a 5-substituted tryptophan unnatural amino acid**.**

Claim 34 has been amended to recite "comprising the sequence of SEQ ID NO: 2 or a conservative variant thereof". The specification as filed defines "Conservative variations" at paragraphs [0092] to [0094] as nucleic acids which encode identical or essentially identical amino acid sequences (see, Table 1). Hence the claimed nucleic acid variants can be modified at any position of the nucleotide sequence of SEQ ID No. 1, provided that they encode conservative amino acid residues. Thus the breadth of claim 34 remains very broad. While one of skill in the art can readily envision numerable species of nucleic acid sequences that are at least a given % identity to a reference nucleotide sequence (e.g., SEQ ID No. 1) that encodes a variant of at least

a given % identity to the amino acid sequence of SEQ ID No. 2, one cannot envision which of these also encode a *B. subtilis* O-muTrpRS with the claimed orthogonal activity (e.g., one catalytically competent in an eukaryotic cell).

The specification provides sufficient guidance in Example 1 for the corresponding pair O-TrpRS/ O-tRNA from *B. subtilis* that can be used to genetically encode an unnatural amino acid (and not endogenous amino acids) in mammalian cells, because the *B. subtilis* O-tRNA is not recognized by any of the aminoacyl-tRNA synthetases in the mammalian endogenous translation system thus preventing aminoacylation of the O-tRNA with endogenous amino acids. Hence Example 1 confirms the inter-species differences in tRNA recognition elements. In other words, *B. subtilis* O-TrpRS can efficiently charge total tRNA isolated from *B. subtilis* including a *B. subtilis* tRNA with mutations of the anticodon loop *(i.e., B. subtilis* $tRNA^{Trp}$). Additionally, Example 2 teaches the uniqueness of orthogonal pair *B. subtilis* orthogonal tryptophanyl-tRNA synthetase (O-muTrpRS)-opal suppressor tRNA ($mutRNA^{Trp}_{UCA}$) after transfecting mammalian 293T cells with three individual plasmids, pTrptRNA, pFoldon TGA (e.g., UGA termination mRNA selector codon) and mutant pEF6-TrpRS (i.e.,Val144ProBsTrpRS), demonstrating that opal suppression (UCA) in mammalian cells depends on expression of the *B. subtilis* orthogonal tryptophanyl-tRNA synthetase (O-muTrpRS)/opal suppressor tRNA ($mutRNA^{Trp}_{UCA}$) pair. Thus, *B. subtilis* orthogonal tryptophanyl-tRNA synthetase (O-muTrpRS) aminoacylates the corresponding *B. subtilis* opal suppressor tRNA ($mutRNA^{Trp}_{UCA}$) with 5-HTPP for suppression of the TGA68 in the mutant foldon construct. In other words, the generation of the *B. subtilis* tryptophanyl-tRNA synthetase (O-TrpRS)-opal suppressor $tRNA^{Trp}$($mutRNA^{Trp}_{UCA}$) pair uniquely incorporates 5-HTTP (e.g., an unnatural amino acid) into a mammalian protein in response to a

UGA termination anticodon and the mRNA selector codon. Thus, the orthogonal *B. subtilis* is pair specific and replacement of one element of the pair such as the *B. subtilis* O-tRNA by other species O-tRNA, e.g., *B. stearothermophilus* t-RNA^{Trp} or *E. coli* t-RNA^{Trp}, would necessitate a different cognate TrpRS to enable the claimed functionality. Clearly, apart from the *B. Subtilis* orthogonal tryptophanyl-tRNA synthetase (O-TrpRS)-opal suppressor tRNA^{Trp} ($mutRNA^{Trp}_{UCA}$) pair, the as-filed specification does not provide sufficient disclosure for selection and use of other conservative variants of SEQ ID NO: 2 (O-muTrpRS) and a genus of unspecified species of O-tRNAs to able to selectively incorporate a 5-substituted tryptophan unnatural amino acid into proteins of eukaryotic cell. There is no description in the specification, as originally filed, of other mutations of other claimed genus of O-tRNA/O-RS pairs wherein the O-RS uniquely recognizes the O-tRNA and selectively charges it with a 5-substituted tryptophan unnatural amino acid, as embraced by the claim limitations. Hence, there is not indication of a structure-function relationship between a genus of O-RS nucleic acid sequences encoding conservative variants SEQ ID NO: 2 and the claimed genus of species of the O-tRNA, other than tRNA^{Trp}($mutRNA^{Trp}_{UCA}$) for the preferential aminoacylation of the O-tRNA^{Trp} with a 5-substituted tryptophan unnatural amino acid so as for the acylated RNA to insert the 5-substituted tryptophan unnatural amino in response to the unique opal suppressor codon.

Response to Applicant Arguments as they apply to rejection of Claims 34-55 and 62-67 under 35 U.S.C. 112, first paragraph.

At pages 8 and 9 of Remarks, Applicants essentially argue that sufficient guidance has been provided in the disclosure to allow a high degree of success in conservative substitutions of the claimed genus of O-tRNA/O-RS pairs. Moreover at page 10 of Remarks, Applicants contend

that the structure of synthetase and tRNA are well known in the art due to more than 50 years of intense studies. Applicants cite the generation of the *B. subtilis* O-muTrpRS mutant wherein a Val was replaced by a Pro at position 144 to accommodate 5-substituted tryptophan analogs in the active site. The location of said substitution, Applicants allege, identified functions of His 44 and Asp133, tRNA conserved residues, suggested modifications, and warnings on residues not to change as stated in the specification at paragraphs 140 and 179 and Figures 1 and 5. Furthermore, Applicants allege that the Office has cited findings that express amazement at single amino acid substitutions in an active site that abrogates the activity of an enzyme. However, Applicants allege that is hard to find rate mutations that destroy functionally. As such, Applicants allege that the enablement is clearly appropriate in this case. Such is not persuasive.

Paragraph 140 refers to well known elements in the tRNA sequences of prokaryotes and eukaryotes that influence expression activity and specifity of tRNA enzymes. The disclosure does not provide sufficient guidance for the twenty one cognate amynoacyl-tRNA synthetase-suppressor tRNA pairs to be used in site-specific incorporation of amino acid analogs into proteins in prokaryotes and eukaryotes. The disclosure merely amounts to an invitation for the skilled Artisan to try and follow the disclosed instructions of known motifs of tRNA synthetase and tRNA to make and use the claimed orthogonal pair of the invention. How can such a broadly claimed evaluation step be performed without an undue experimentation when there is no supporting evidence to substantiate a reasonable correlation of how any of the amynoacyl-tRNA synthetase aminoacylates the corresponding suppressor tRNA and no other endogenous tRNA in the cell, or how a suppressor tRNA is not aminoacylated by any of the endogenous amynoacyl-tRNA synthetase in a method that specifically incorporates a 5-subtituted tryptophan unnatural

amino acid in any host system (e.g., prokaryote or eukaryote) ? Moreover, the specification clearly discloses that despite knowledge of the active site in the *B. subtilis* tryptopanyl-tRNA synthetase (BsTrpRS) determined by comparison to the structure of highly homologous nucleotide sequence of a *Bacillus stearothermophilus* tryptophanyl-tRNA synthetase (paragraphs [0178]-[0179]), it was "somewhat surprising that a single mutation at the active site of BsTrpRS completely altered its specificity from L-tryptophan to 5-HTPP" ([paragraph [0182]). This result further underlines the unpredictability of how identified substitution in the active site of a highly homologous structure enzyme which are expected to interact with other residues in the binding pocket completely changed the activity of the *Bacillus* RS. Indeed, the art further corroborates that single mutations in an active site can completely alter, e.g. abrogate functionality, independently from contemplated interactions with other functional residues (Biochemistry, John Wiley and Sons, 1990, p. 126-129). In addition, paragraph 170 cited by Applicants, merely recites the generation of the O-RS/O-tRNA orthogonal pairs taking advantage of inter-species differences in tRNA recognition elements, particularly the knowledge that *B. subtilis* $tRNA^{Trp}$ is generally not a substrate for the tryptophan-tRNA synthetases from yeast and mammalian cells, clearly indicating that *B. subtilis* $tRNA^{Trp}$ was the starting point of the invention as it appears to be orthogonal to mammalian cells. No disclosure of other *B. subtilis* tRNA cross-species tRNA anticodon specifity or tRNA cross-species tRNA specifities of synthetases are disclosed, let alone any tRNA (other than *B. subtilis* tRNA) cross-species tRNA specifities of synthetases for site-specific incorporation of 5-subtituted tryptophan unnatural amino acid. In contrast to applicants' opinion, there is not evidence that any nucleic acid sequence encoding an orthogonal conservative variant of SEQ ID NO: 2 (O-muTrpRS) would efficiently charge an O-tRNA from

any species with a 5 substituted tryptophan unnatural amino acid into a peptide in an eukaryotic host cell.

At pages 12 and 13 of remarks, Applicants essentially list all the sources available to the skilled artisan for guidance including "paragraphs 140 and 183, materials and methods starting at paragraph 159, and Figures 1 and 5. Alternate resources for system components are identified (see, paragraphs 37, 86, and 88) as are conservative substitutions (see, paragraph 93 and Table 1). Also included are extensive citations of references (e.g., Anderson et al., (2002) Exploring the Limits of Codon and Anticodon Size, Chemistrv and Biology, 9:237- 244; GENBANK; computer-assisted modeling Macromodel version 8.1, Schrodinger, LLC; U.S. Patent Application No. 10/126,927, "In Vivo Incorporation of Unnatural Amino Acids", by Shultz, et al., and U.S. Application No. 10/126,931, "Methods and Compositions for the Production of Orthogonal tRNA - Aminoacyl tRNA Synthetase Pairs" by Shultz, et al.)" . Specifically, at page 13 of remarks, Applicants cite Liu et al., (PNAS, pp. 4780-4785, at 4782) allegedly providing support for the contention that if the skilled artisan can identify a functional system by mutation of a non-functioning system (as in Liu), it would be easier for one of skill to identify a functional systems from mutants starting with a functional system, as in the instant invention where applicants have already provided a functional structure i.e. RS SEQ ID No. 2. As such, applicants argue one of skill would identify logical conservative substitutions, within the limitations of the claims, retaining substantial functionality without undue experimentation. Such is not persuasive.

As stated in the paragraph above, the specification as filed defines "conservative variations" at paragraphs [0092] to [0094] as nucleic acids which encode identical or essentially identical

amino acid sequences (see, Table 1). Hence the claimed nucleic acid variants can be modified at any position of the nucleotide sequence of SEQ ID No. 1. While one of skill in the art can readily envision numerable species of nucleic acid sequences that are at least a given % identity to a reference nucleotide sequence (e.g., SEQ ID No. 1) that encodes a variant of at least a given % identity to the amino acid sequence of SEQ ID No. 2, one cannot envision which of these also encode a *B. subtilis* O-muTrpRS with the claimed orthogonal activity (e.g., no catalytically competent in an eukaryotic cell). The Liu reference specifically discloses an "orthogonal" suppressor tRNA derived from *Saccharomyces cerevisiae* $tRNA_2^{Gln}$ which is not a substrate *in vitro* or *in vivo* for any *Escherichia coli* aminoacyl-tRNA synthetase, including *E. coli* glutaminyl-tRNA synthetase (GlnRS). Thus the yeast $tRNA_2^{Gln}$ /yeast GlnRS thus represents a completely orthogonal tRNA/synthetase pair in *E. coli* suitable for the delivery of unnatural amino acids e.g., majority of glutamine and glutamic acid analogs, into proteins *in vivo*. Hence, the Liu reference is merely one orthogonal pair for use in *E. coli* from the yeast $tRNA_2^{Gln/}$ yeast GlnRS pair. There is no evidence that the same yeast $tRNA_2^{Gln}$ / yeast GlnRS is orthogonal to eukaryotic cells nor that the $tRNA_2^{Gln}$ / yeast GlnRS can incorporate 5- substituted tryptophan in *E. coli.* Applicants' argument of whether is easier to identify a functional system by mutation of a functioning system, are not on point. The skilled artisan will have to test each prospective orthogonal suppressor tRNA/amynoacyl-tRNA synthetase pair for site-specific incorporation of 5- substituted tryptophan (e.g., unnatural amino acids) into proteins in the target host, thus undue experimentation would be required to practice the invention as it is claimed in its current scope.

At page 14 of remarks, in relation to the state of the art and relative skill of those in the art, Applicants essentially contend that a wide variety of tRNA synthetases were known at the time

the invention was filed with some web list disclosing over 1,000 available synthetase, including well over 100 for which the three dimensional crystal structure has been determine. As such applicants allege that one of skill knew functions of RS structures at the time, so could have practice functional variants of a given structure without undue experimentation. Additionally, Applicants argue that " one of skill can have high confidence in substituting one amino acid known to cooperate in a helix stabilization (e.g., alanine) with another amino acid known to cooperate in a helix stabilization (e.g., leucine) with high confidence in retaining functionality of the peptide. This particularly when conserved structures, such as binding pockets and active sites have been identified (as in the present invention). Again, Applicants note that, even without systematic protection of conserved structures, and structures identified as to function, one of skill could predictably screen for functional variants of the provided sequences, even from a randomly mutated library. The predictable success rate would jump astronomically were the mutations logically directed in recognition of functional structures known in the art and provided in the present specification". Such is not persuasive.

As stated in the paragraph above, the instant invention is not merely drawn to an amynoacyl-t tRNA synthetase or tRNA but to a very specific orthogonal amynoacyl- tRNA synthetase pair (i.e., muTrpRS of SEQ ID No. 2/ O-tRNA of SEQ ID NO: 3) for site-specific incorporation of 5- substituted tryptophan unnatural amino acids into proteins in the target host. The art discloses the specifity of orthogonal functional tRNA/pairs to uniquely charge specific unnatural amino acid in a host cell which requires importing a suitable pair from another organism or modifying the endogenous pair, so that the O-tRNA is not recognized by any of the endogenous aminoacyl-tRNA synthetases in the host endogenous translation system. For

example, differences in tRNA recognition between species is demonstrated when nonsense amber suppressors derived from $tRNA^{tyr}$ is charged with tyrosine in *E. coli* but leucine in yeast (Ulmasov, 1998, Nucleic Acid Research, pp. 5139-5141, Abstract). Applicants have not provided any evidence that the orthogonal mutant tryptophanyl-tRNA synthetase of SEQ ID No. 2 can exhibit suppressor activity with orthogonal t-RNA^{Trp} from any species, much less any t-RNA to charge a 5- substituted tryptophan unnatural amino acid. Likewise, there is not evidence that conservative variants of SEQ ID No. 2 can exhibit suppressor activity with orthogonal t-RNA^{Trp} from any species, much less any t-RNA.

New Grounds of Objection/Rejection

Claim Objections

Claim 66 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Specifically, claim 66 which depends on claim 34 encompasses an O-muTrpRS consisting of residues Asp140, He141, Val142, Pro143, Gly145, and amino acid other than Val at a position corresponding to position 144. However, the O-muTrpRS of claim 34 comprises a proline residue at a position corresponding to position 144 of SEQ ID NO: 2, generated by replacing a Val-144→Pro. Thus the O-muTrpRS of claim 66 having an amino acid other than Val at position 144 fails to further limit the structure of the O-muTrpRS.

Conclusion

Claims 34-55 and 62-67 are rejected.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is

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